Review

The gut microbiome: what every gastroenterologist needs to know

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ABSTRACT

The mucosal surfaces of the body are characterised by complex, specialised microbial communities, often referred to as the *microbiome*. However, only much more recently—with the development of technologies allowing exploration of the composition and functionality of these communities—has meaningful research in this area become feasible. Over the past few years, there has been rapid growth in interest in the gut microbiome in particular, and its potential contribution to gastrointestinal and liver disease. This interest has already extended beyond clinicians to pharmaceutical companies, medical regulators and other stakeholders, and is high profile among patients and the lay public in general. Such expansion of knowledge holds the intriguing potential for translation into novel diagnostics and therapeutics; however, being such a nascent field, there remain many uncertainties, unanswered questions and areas of debate.

INTRODUCTION

There is a need for gastroenterologists and hepatologists to have an understanding of some of the key principles underlying the gut microbiome, given the implications it has for clinical medicine and the considerable interest that it increasingly holds for patients. The fast-moving nature of the field and sometimes complex terminology can create confusion. This review aims to give an overview of the central areas of knowledge about the gut microbiome, as well as highlighting the major future directions in this area.

OVERVIEW OF THE GUT MICROBIOME

What is the 'microbiome' and 'microbiota'?

First coined by Joshua Lederberg in 2001, these terms are often used interchangeably. The human microbiota consists of up to 100 trillion microbial cells harboured by an individual, whereas the microbiome is the catalogue of these microbes and their genes living within a specific niche such as the human gut (table 1).[1] The key technology used to study the composition of the gut microbiome is next-generation sequencing of bacterial genomes, using DNA extracted from samples (eg, stool, colonic mucosal biopsies) as starting material. This may be done using different techniques, each with their own associated strengths and weaknesses, but all relying on the principle of comparing the DNA sequences obtained from a biofluid with reference databases of microbial genomes (table 2). Bioinformatic tools then help to identify the specific bacterial taxonomic composition within the sample.[2 3] However, while these sequencing technologies are very helpful for identifying 'what is there' in a sample, this does not give the full perspective as to what these bacteria are doing functionally, and how they are interacting with their mammalian host. As such, study of microbiome composition is now often supplemented by other systems biology techniques that give insight into microbiome function, such as metabonomics and proteomics (figure 1); these are also reviewed elsewhere.[2 3]

Acquisition of the gut microbiome remains controversial, with the most robust evidence suggesting that it is a dynamic process that starts immediately after birth.[4] The first (and most critical) contribution to the establishment of a microbiome is the vertical transmission of maternal microbiome at the time of birth. The specific patterns of colonisation of the gut microbiome within the first few weeks of life are thought to have crucial effects on its future composition.[5 6] Following this, the infant gut microbiome undergoes rapid development over the first year of life, and appears to be established in an adult form by 3 years of age. Multiple factors play a key role in determining the

Table 1 Glossary of common terms related to the gut microbiome

Term	Further details
Gut microbiota	The total assemblage of microorganisms present within the gut mucosal environment.[1]
Gut microbiome	The entire gut ecological habitat, including the microorganisms themselves, as well as their genomes, and the surrounding environmental conditions.[1]
Dysbiosis	A term still used commonly to describe perturbation of the composition of the gut microbiome compared with what might be expected in the healthy host. However, in reality, often a poorly descriptive term without a specific biological definition.
Pathobiont	Microorganisms that usually interact with the host symbiotically, but have the potential to act as pathogens and cause disease under certain conditions.
Faecal microbiota transplant (FMT)	Typically, a liquidised suspension of microbes (and their associated environmental *milieu*) derived from manipulated whole stool, administered to the gut of affected patients. Stool is obtained from healthy screened donors, and prepared using homogenisation, mixing with a diluent (eg, normal saline) and filtration. However, lyophilised FMT preparations are now also increasingly being used.

gut microbial composition during its development, starting from mode of delivery (vaginal vs caesarean), to early feeding (breast vs formula), use of antibiotics in early life, diet and the environment.[7–9]

Of all the environmental influences on the gut microbiome, the contribution of diet is among the most important. It is well-established that diet can rapidly and reproducibly alter the gut microbiome, making human studies which do not control for diet difficult to interpret, and also implicating diet as a therapeutic target for altering the gut microbiome.[10]

What is the significance of a gut microbiome?

The gut microbiome is not a bystander, and has co-evolved with the host over thousands of years to form a complex and mutually beneficial relationship. Through this relationship, the microbiome provides a multitude of benefits to the host, including shaping the intestinal and systemic immune system,[11] maintaining the healthy intestinal epithelium, harvesting energy from food[12] and protection against pathogens.[13] The alteration of the composition of the microbiome that results in disruption of these important physiological functions has sometimes been referred to as 'dysbiosis'.

What is 'dysbiosis'?

Dysbiosis is used to describe a change in diversity of microbiome, loss of specific beneficial microbes (symbionts) and expansion of potentially harmful ones (pathobionts). It is, however, a very non-descriptive and perhaps unhelpful term that often gets used to describe any shift in the gut microbial composition away from that seen in a 'healthy host' despite there being no agreed definition of what a 'healthy gut microbiome' is.[14] The gut microbiome is largely composed of two groups at the phyla level, being dominated by the obligate anaerobic Bacteroidetes and Firmicutes, which make up 90% and are generally associated with health (beneficial). Other phyla present at lower levels are Actinobacteria, Fusobacteria, Verrucomicrobia and Proteobacteria, facultative anaerobes. The latter phylum comprises the common Gram-negative pathobionts such as *Salmonella* spp, *Shigella* and *Escherichia coli*. Despite uncertainty regarding the normal microbiome, remarkably congruent signals of 'dysbiosis' have been described (at least at a high taxonomic level) for nearly all chronic gastrointestinal (GI) and liver diseases including inflammatory bowel disease (IBD),

Table 2 Overview of common modalities of microbiome sequencing

Name of technique	Overview	Strengths	Drawbacks
Metataxonomics (16S rRNA gene sequencing)	► The 16S rRNA gene is present in all prokaryotes, and consists of highly conserved regions interspersed by nine 'hypervariable' regions. Hypervariable regions are of variable sequence and length between different bacteria. ► As such, PCR amplification and DNA sequencing of different bacterial 16S rRNA genes within a biofluid can allow identification of the different bacteria within samples.	► This is now a well-established, high-throughput technique, which is relatively cheap compared with alternatives.	► This technique may give detail down to bacterial genus level, but rarely gives any greater resolution than this. ► There are a number of factors that can bias the results obtained, for example: – There is variable use of primers, PCR conditions and analytic approach between different centres. – Different bacteria have different copy numbers of the 16S rRNA gene, influencing the apparent relative abundance of certain bacteria within a sample.
Shotgun metagenomics	► This technique involves fragmentation and random sequencing of DNA from the collection of genomes and genes within the sample, and the use of advanced bioinformatic techniques to analyse the sequencing data obtained.	► Shotgun sequencing regularly gives characterisation down to species (and even possibly strain) level resolution. ► Since this technique sequences bacterial genes, it also gives insight into the microbial functionality of a sample.	► Gaps in knowledge in the accuracy and completeness of reference microbial genomic databases means large portions of sequencing data may be difficult to interpret. ► Datasets are large and complex, and experiments are much more expensive than metataxonomics. ► As per metataxonomics, there are still outstanding issues related to factors which may bias results.

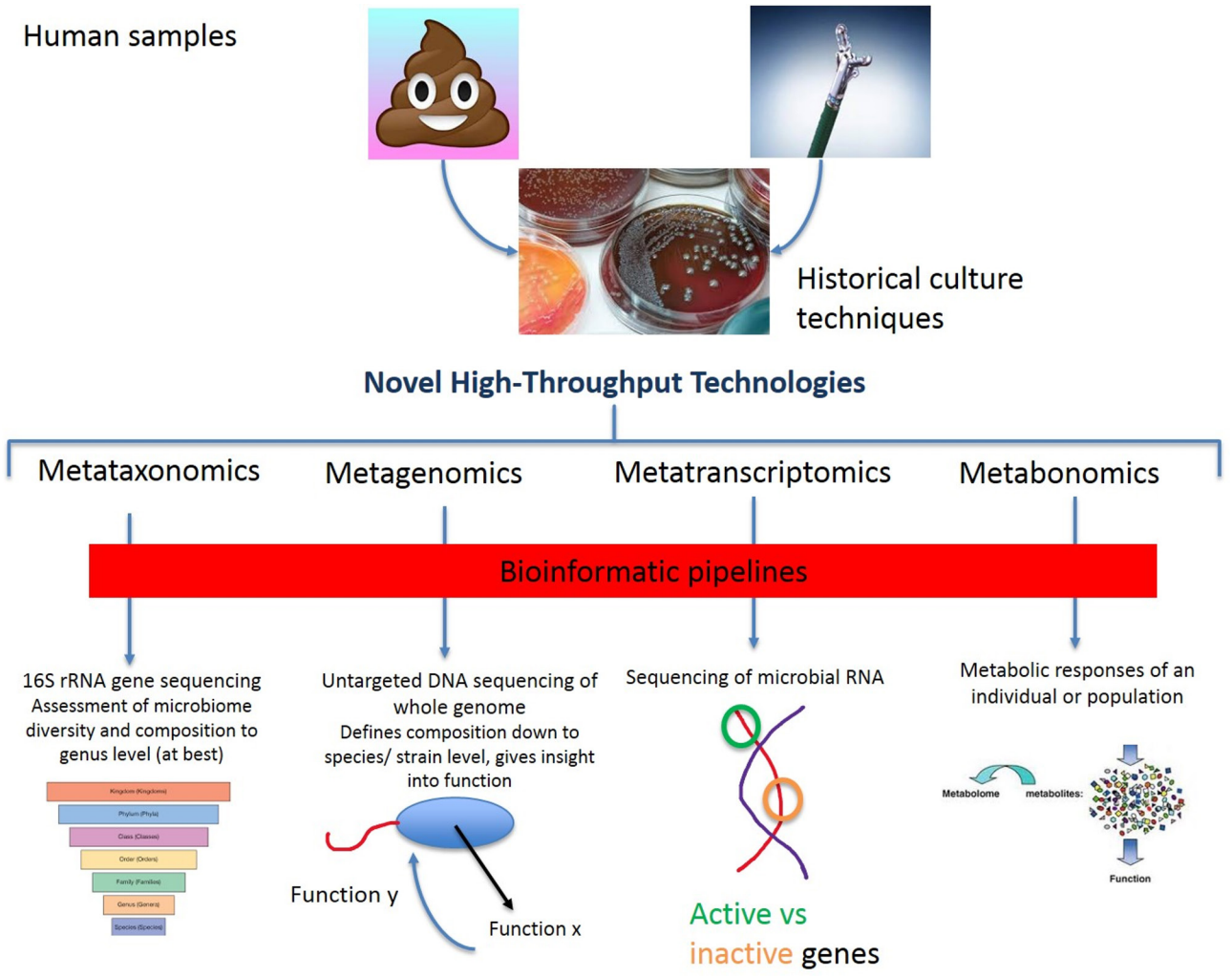

Figure 1 Conventional and novel techniques for studying the gut microbiome. Traditional culture methods have drawbacks when applied to characterising the gut microbiome, as many species present are strictly anaerobic and not easily amenable to culture. The development of culture-independent DNA sequencing techniques has given insight into the composition of microbial communities; these are increasingly coupled with other techniques which elucidate microbiome functionality, such as metabonomics. This figure summarises the major culture-independent techniques in current use.

irritable bowel syndrome (IBS), primary sclerosing cholangitis and non-alcoholic fatty liver disease.[15] It should however be emphasised that in most cases, dysbiosis merely shows an association rather than a cause. Furthermore, there is also increasing evidence to support a significant but less well-characterised contribution from the microbial communities of viruses and fungi (often referred to as the '*virome*' and '*mycobiome*', respectively).[16 17]

THE CONTRIBUTION OF THE GUT MICROBIOME TO DISEASE: SPECIFIC EXAMPLES

Introduction

There are an ever-growing number of observational studies that have identified distinctive differences in the gut microbiome between patients with particular conditions and matched controls. Such changes are complex and nuanced, and are typically influenced by severity and distribution of disease, underlying treatment at the time of sampling, and region of the world in which the study is being performed, among other factors. However, in this section, a general summary is given of the key microbiome changes that accompany major GI and liver conditions.

Clostridioides difficile infection

Clostridioides difficile is a Gram-positive sporulating obligate anaerobe belonging to the Firmicutes phylum. This can sometimes apparently be a normal component of the healthy gut microbiome, but in the context of treatment with broad-spectrum antibiotics, the colonic microbiome is damaged, with an almost total loss of Bacteroidetes, reduction in Firmicutes and an overgrowth of Proteobacteria; these changes allow *C. difficile* spores to germinate and for growth (and subsequent toxin production and infection) to occur .[18] The contribution of faecal microbiota transplant (FMT) to restoration of the gut microbiome and treatment

of *C. difficile* is discussed in 'The gut microbiome as therapy' section.

Inflammatory bowel disease

Congruent signals with regard to microbiome disruption are seen in ulcerative colitis (UC) and Crohn's disease (CD). It is well-recognised that there is a loss of bacteria belonging to the Firmicutes phylum[19] and most studies (although not all) show the same with respect to Bacteroidetes.[19–21] *Faecalibacterium prausnitzii* has often been highlighted as a bacterial species which can ferment non-absorbed dietary components into compounds beneficial to the host called short chain fatty acids; *F. prausnitzii* is reduced in prevalence in both CD and UC.[22] Data have suggested that alteration in the gut microbiome plays a central role in driving UC; datasets highlighting the importance of *Roseburia hominis*,[23] *F. prausnitzii*[24] and *Akkermansia muciniphila*[24] in the inflammation in UC have been published. An over-representation of Gram-negative pathobionts has been described in the gut microbiome of people with IBD,[19] with species of note being *E. coli*[25] and *Fusobacterium* spp.[26]

There are a lack of inception data in IBD, which leaves the question of which is the 'chicken' and which the 'egg' with respect to dysbiosis and inflammation/treatment effects in the context of IBD. This was partially addressed by Gevers *et al*,[27] who examined a large cohort of treatment-naïve children with new-onset CD. They were able to show a clear difference in the gut microbiome in this cohort compared with healthy controls, and therefore make a link between disease severity and dysbiosis. Recent efforts towards unravelling causal relationships were explored in a study that demonstrated induction of colitis in germ-free mice following transplantation of stool from patients with IBD.[28]

Regarding the 'IBD microbiome', much remains to be discovered regarding the contribution of non-bacterial components of the microbiome (such as phages and fungi), the effect of host genetics on the microbiome and mechanisms underlying the observed observations.

Ileal pouch anastomosis

Up to 40% of patients who undergo ileal pouch anastomosis (IPAA) following subtotal colectomy for UC will experience pouchitis within 5 years. It is now established that the microbiome in the pouch is the trigger for this, and broad-spectrum antibiotics are very effective for acute pouchitis.[29] However, 10%–15% will go on to have chronic pouchitis, which may or may not respond to current therapy.[30]

The bacterial community present in the ileal mucosa starts to resemble that of the colon immediately after ileostomy closure,[31] and this microbial dysbiosis is associated with the development of pouchitis.[32] Comparing non-inflamed with inflamed pouches, the latter show reduced microbiome diversity, similar but somewhat more pronounced than that seen comparing the bacterial diversity seen in UC compared with normal colon. In particular, in pouchitis, Bacteroidetes are reduced, whereas members of the Proteobacteria family are relatively increased.[33] More recently, it was demonstrated that certain bacterial genera (*Blautia, Dorea, Moryella, Suterella* and *Bacteroides*) are associated with a better outcome in relation to treatment in patients with pouchitis.[34] Furthermore, again similar to the situation in UC, it seems that generally, a reduction in families of the Firmicutes phylum and an increase in Proteobacteria are associated with inflammation. It appears that the microbiome dysbiosis seen in pouches is similar when comparing newly formed with more mature pouches.[35] Recently, in a prospective study of 19 patients undergoing colectomy and IPAA, 43% developed pouchitis in a year. Interestingly, in these patients, the microbiome in the colon prior to colectomy was highly predictive of the development of pouchitis.[34]

Liver disease

Perturbation of the gut microbiome has been demonstrated in liver diseases including non-alcoholic steatohepatitis/non-alcoholic fatty liver disease, alcoholic hepatitis, primary sclerosing cholangitis, cirrhosis and hepatocellular carcinoma. This is an active area of interventional research using FMT.[36] A recent open-label pilot study of FMT to treat patients with hepatic encephalopathy has shown an interesting signal regarding potential improvement in cognition.[37] An association between specific toxin-producing bacteria and alcoholic hepatitis has recently been described, and bacteriophages were shown as a targeted route to remove these bacteria and possibly reverse alcohol-related liver disease in a rodent model.[38]

Irritable bowel syndrome

Dysbiosis has been shown between patients with IBS and healthy controls, with a change in the Firmicutes-to-Bacteroides ratio and reduction in bacterial diversity,[39] although certain recent data did not confirm this finding.[40] As such, further research is needed to understand the significance of the contribution of the gut microbiome to IBS.

Colon cancer

Association studies in human cohorts have strongly associated several bacterial species with colon cancer.[41] *Bacteroides fragilis* and *E. coli* have both been implicated, but the predominant bacterial species linked with colon cancer has been *Fusobacterium nucleatum*.[42] This has been associated with a worse phenotype[43] and prognosis.[44] *F. prausnitzii* has been found to be under-represented in patients with human colon cancer.[45] Guo *et al* examined the use of bacterial species as biomarkers to differentiate patients with colon

cancer from controls with benign GI disease (polyps and IBD) and healthy controls.[46] They looked at ratios of *F. prausnitzii*/*F. nucleatum* and *F. nucleatum*/Bifidobacterium. Interestingly, *F. nucleatum*/Bifidobacterium was found to be highly discriminatory versus all controls, raising the possibility of a microbiome-based biomarker for colon cancer. Further larger studies are needed, including interventional studies in humans.

Immune checkpoint inhibitor complications

It is well-established from animal models that responsiveness to treatment with checkpoint inhibitors is dependent on baseline microbiome profile[47] and the impact of human gut microbiome on the efficacy and side-effect profile of anticancer therapies has also been recognised.[48 49] Three recent independent studies on humans with solid tumours undergoing checkpoint inhibition showed the remarkable treatment responsiveness of the patients depending on baseline microbiome, although a consistent signal was not seen; this perhaps reflects the differing methodologies employed in these studies, or may reflect a focus on microbiome composition rather than functionality.[50–52] While it appears that the composition of the gut microbiome is important in laying the foundation for successful checkpoint inhibitor treatment, another aspect of this treatment in which the microbiome seems key is toxicity. Diarrhoea is the main side effect of this highly effective cancer treatment, affecting 40% patients. Of these, a significant proportion go on to develop severe colitis, presumably related to the unfettered action of pro-inflammatory T cells. There have been several intriguing case series where FMT has been shown to be of great benefit in the setting of refractory checkpoint inhibitor colitis,[53] and this is the subject of ongoing randomised trials.

THE GUT MICROBIOME AS THERAPY

Dietary manipulation of the gut microbiome

Detailed discussion of this area is outside the remit of this review, although this is a growing area of interest. In particular, there is an expanding field of research demonstrating that the efficacy of established dietary interventions for GI disease—including the low fermentable oligo, di, mono-saccharides and polyols (FODMAP) diet[54] and enteral nutrition for active CD[55] may be partly mediated by alterations in the gut microbiome.

Prebiotics

Prebiotics are dietary components that are fermentable, which have a health benefit to their host. The most common of these are non-absorbable dietary fibres. They have been specifically defined as 'selectively fermented ingredients that allow specific changes, both in the composition and/or activity of the GI microflora that confers benefits on host well-being and health'.[56 57] Prebiotics are neither hydrolysed nor absorbed in the upper GI tract, but are selectively fermented by intestinal bacteria, and are able to alter the colonic bacteria.[56 58] Animal models have shown that prebiotics can enhance mucosal integrity, and furthermore have been shown to reduce pro-inflammatory cytokines and reduce colitis.[59] Prebiotics have an overall excellent safety profile but can be associated with abdominal pain, flatulence and diarrhoea at high doses.[60] Specific prebiotics—such as the short chain fatty acids, including butyrate, acetate and propionate—have demonstrated benefits for reducing inflammation in IBD.[61]

Probiotics

Probiotics are live microorganisms that, when administered, are intended to have a beneficial effect on the intestinal microbiome, and therefore confer a health benefit effect. Animal models have suggested that probiotics help promote the intestinal barrier.[62] The studies to date looking at probiotics in IBD have been quite mixed, with some studies highlighting that both maintenance of remission or induction of remission could be achieved with probiotics, with others showing little or no benefit in IBD.[63] A systematic review in 2017 suggested that VSL#3 may be effective in inducing remission in active UC. Probiotics may be as effective as 5-ASAs in preventing relapse of quiescent UC, but currently, the efficacy of probiotics in CD remains uncertain.[64] The British Society of Gastroenterology (BSG) guidelines conclude that probiotics may have modest benefits in UC but are not recommended in CD.[64] Importantly for patients with pouchitis, VSL#3 has been shown to be effective in preventing pouchitis and maintaining remission after antibiotic treatment.[65] Multistrain probiotics have shown to be effective for treatment of IBS,[66] and have been recommended for use in a recent American Gastroenterological Association monograph on IBS management; however, this same monograph recommended that prebiotics were not used for this indication.[67]

Faecal microbiota transplant

Overview

Initial studies of FMT for recurrent *C. difficile* infection (CDI) were observational, but these have now extended to a number of randomised trials since 2013. These studies have collectively demonstrated that a single FMT for recurrent CDI has an efficacy of >80% in causing remission from the condition almost regardless of many variables related to administration, including whether upper GI or lower GI administration is used.[68] FMT may also have superior efficacy compared with either vancomycin or fidaxomicin in the treatment of CDI.[69] Other developments over this time have been the development of 'frozen' FMT protocols (allowing FMT to be pre-prepared and stored in freezers until the time of need),[70] and the emergence of FMT capsules.[71]

Summary of indications and procedure for requesting FMT for CDI in UK

Indications:

- **Refractory CDI** – ongoing CDI-related symptoms despite appropriate extended antimicrobial therapy.
- **Recurrent CDI -** ≥ 2 recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe complicated CDI.
    - Patients would typically already have tried therapies recognised to reduce the rate of CDI recurrence (i.e. extended/ pulsed vancomycin and/or fidaxomicin, or bezlotoxumab) prior to considering FMT.

N.B. Coexisting IBD and/or immunodeficiency are not contraindications for receipt of FMT, but administration in such patients requires careful consideration.

Current FMT providers in the UK:

Different arrangements in different regions of UK, but includes Imperial College Healthcare NHS Trust, Guy's and St Thomas' NHS Trust, EnteroBiotix, and University of Birmingham, i.e.:

- University of Birmingham Microbiome Treatment Centre (UoBMTC); contact via bhs-tr.FMT@nhs.net or +44 (0)121 414 4547.
- *FMT is provided to the clinicians within 1-2 working days of receipt of the completed FMT request form.*

Assessment of response

Response to FMT in the form of resolution of diarrhoea is usually seen within 3-5 days. We would recommend repeating FMT if no response is seen after 1 week of treatment. Routine laboratory testing for *C. difficile* toxin after FMT is not recommended, but it is appropriate to consider in the case of persistent CDI symptoms/suspected relapse.

FMT checklist for treatment of CDI

Before FMT:

- Check and confirm formal consent.
- Stop antibiotics 12-24 hours before.

Upper GI delivery of FMT:

- Consider administering PPI and prokinetic before FMT.
- Bowel lavage may be given before FMT.
- Insert NG tube before procedure and confirm position.

Lower GI delivery of FMT:

- Administer bowel lavage before FMT.
- Consider loperamide immediately before or after FMT.

After FMT:

- Common effects include bloating, nausea and constipation.
- Monitor and report adverse events specifically vomiting, aspiration, fever and sepsis.

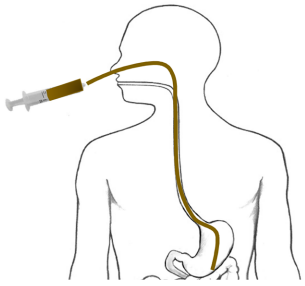

Figure 2 Summary of key considerations related to administration of faecal microbiota transplant (FMT) for treatment of recurrent CDI. As adapted from the British Society of Gastroenterology and Healthcare Infection Society FMT guidelines.[74] CDI, *Clostridioides difficile* infection; GI, gastrointestinal; IBD, inflammatory bowel disease; NG, nasogastric.

While regulation of FMT has been approached differently in various countries, FMT regulation in the UK is within the remit of the Medicines and Healthcare products Regulatory Agency (MHRA), who regulate it as a medicinal product. Within the UK, FMT for recurrent CDI has also been approved by the National Institute for Health and Care Excellence[72] and Public Health England[73]; best practice regarding all aspects of FMT preparation and administration—as well as donor selection, care of the recipient and governance aspects of running FMT services—have recently been described in joint BSG/Healthcare Infection Society guidelines.[74] European[75] and US[76] guidelines addressing the role of FMT in the treatment of recurrent CDI have also been published. Key best practice aspects of FMT administration are summarised in figure 2.

Donor selection is an area that has been particularly high profile of late, given the described transfer of an extended-spectrum beta-lactamase-producing *E. coli* from donor to two FMT recipients in the USA, with bacteraemia occurring in both patients, and one of the patients dying.[77] The protozoan intestinal parasite *Blastocystis* has also been shown to be transmissible via FMT in humans.[78] Given some of the complexities in running FMT services (including logistics related to maintaining a donor pool, costs in screening and preparing material, need for sufficient freezer capacity, etc), there is a growing interest in 'stool banks', whereby a 'hub' centre provides FMT to 'spoke' centres.[79]

However, there are still gaps in knowledge related to FMT for the treatment of recurrent CDI. While FMT appears relatively safe over the short term, it is unknown if there are any potential long-term sequelae related to gut microbiome manipulation; the development of FMT registries in certain countries (including the USA and Germany) is an attempt to monitor for this. Furthermore, mechanisms of action of FMT remain poorly understood, although there has been progress made in this area of late.[80]

FMT in the non-CDI setting

There have been four randomised studies using FMT as treatment for UC; these have collectively demonstrated that FMT appears to be a relatively safe and effective modality for induction of remission for this condition (OR=2.89, 95%CI=1.36 to 6.13, p=0.006).[81 82] However, these studies are markedly heterogenous with regard to key variables (including number of treatments, and mechanics of preparation

Table 3 Summary of studies of FMT in non-CDI conditions

Study condition	Summary of outcomes from clinical studies
Inflammatory bowel disease	Four randomised studies have collectively demonstrated FMT to be relatively safe and effective in inducing remission in mild-to-moderate UC. However, the relatively small size of trials and heterogeneity in their design has limited interpretability and applicability, and FMT is not currently recommended for this indication.[74]
Primary sclerosing cholangitis[87]	In a pilot study, 3/10 patients receiving FMT experienced a ≥50% decrease in ALP levels. There was correlation between bacterial taxa in the stool microbiome post-FMT and ALP levels.
Obesity[88]	In patients with obesity (but no other features of metabolic syndrome), no weight loss or change in GLP-1 levels were seen after FMT. However, stool microbiome and bile acid profiles were altered.
Metabolic syndrome[89–91]	FMT was associated with a transient improvement in peripheral insulin resistance, but this was not sustained. Furthermore, FMT from patients with metabolic syndrome into recipients with metabolic syndrome themselves resolved in transient worsening of insulin resistance.
Autism[92]	
Intestinal decolonisation of multidrug-resistant organisms[93]	There are a growing number of case reports and case series suggesting that FMT may decolonise multidrug-resistant bacteria from the gut; however, a randomised controlled trial showed no difference in decolonisation rates between patients receiving FMT and those receiving no intervention.
Hepatic encephalopathy[37]	Patients receiving FMT (while receiving lactulose and rifaximin) may have fewer hospital admissions with encephalopathy compared with those receiving medical therapy alone.
Irritable bowel syndrome[84 85]	Variable results in the randomised studies performed to date, with overall disappointing outcomes. However, this may reflect heterogeneity of study design.

ALP, alkaline phosphatase; CDI, *Clostridioides difficile* infection; FMT, faecal microbiota transplant; GLP-1, glucagon-like peptide-1; UC, ulcerative colitis.

and administration), limiting their interpretability and applicability. Within the UK, the multicentre STOP-Colitis trial is ongoing, which is methodologically investigating the optimal route of FMT administration to patients with UC, and further establishing the efficacy of this treatment for the condition.[83]

Results of randomised trials for IBS have been somewhat contradictory but overall disappointing at present, but this may be reflective of aspects of trial design.[84] Further recent data suggest that FMT may have potential as a treatment for IBS, but that appropriate donor selection may be much important than is the case for recurrent CDI.[85] Small single-centre studies of FMT for the treatment of hepatic encephalopathy show promising results,[37] and a UK study investigating the safety of administration of FMT to patients with cirrhosis (Prospective, randomised placebo controlled feasibility trial of faecal mIcrobiota Transplantation in cirrhosis (PROFIT)) has now finished recruitment.[86]

The range of other conditions in which FMT has been reported to be of potential benefit are very wide in scope, including primary sclerosing cholangitis, obesity/metabolic syndrome, autism and in the intestinal decolonisation of multidrug-resistant bacteria[80] (table 3).

CONCLUSION

New technologies to explore the gut microbiome have resulted in major developments in knowledge over a short period of time. The association between a perturbed gut microbiome and a range of different GI and liver diseases is now well-recognised, but whether the microbiome changes are cause, consequence of incidental remains largely unclear while further mechanistic studies are awaited. The success of FMT for the treatment of CDI has created enthusiasm about a new paradigm of 'microbiome therapeutics'. However, it is also clear that there remains layers of complexity and uncertainty in the biology of the gut microbiome that were not initially recognised. These will require careful deconvolution over the coming years in order to enable the maximum potential translation of this knowledge base into clinical benefit.

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REFERENCES

1 Marchesi JR, Ravel J. The vocabulary of microbiome research: a proposal. *Microbiome* 2015;3:31.
2 Segal JP, Mullish BH, Quraishi MN, *et al*. The application of omics techniques to understand the role of the gut microbiota in inflammatory bowel disease. *Therap Adv Gastroenterol* 2019;12:175628481882225.
3 Mullish BH, Osborne LS, Marchesi JR, *et al*. The implementation of omics technologies in cancer microbiome research. *Ecancermedicalscience* 2018;12:864.
4 Rodríguez JM, Murphy K, Stanton C, *et al*. The composition of the gut microbiota throughout life, with an emphasis on early life. *Microb Ecol Health Dis* 2015;26:26050.
5 Gritz EC, Bhandari V. The human neonatal gut microbiome: a brief review. *Front Pediatr* 2015;3.

6 Robertson RC, Manges AR, Finlay BB, *et al*. The human microbiome and child growth – first 1000 days and beyond. *Trends Microbiol* 2019;27:131–47.
7 Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol* 2019;16:35–56.
8 Francino MP. Antibiotics and the human gut microbiome: Dysbioses and accumulation of resistances. *Front Microbiol* 2016;6.
9 Salminen S, Gibson GR, McCartney AL, *et al*. Influence of mode of delivery on gut microbiota composition in seven year old children. *Gut* 2004;53:1388–9.
10 David LA, Maurice CF, Carmody RN, *et al*. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014;505:559–63.
11 Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol* 2016;16:341–52.
12 Tremaroli V, Kovatcheva-Datchary P, Bäckhed F. A role for the gut microbiota in energy harvesting? *Gut* 2010;59:1589–90.
13 Libertucci J, Young VB. The role of the microbiota in infectious diseases. *Nat Microbiol* 2019;4:35–45.
14 Olesen SW, Alm EJ. Dysbiosis is not an answer. *Nat Microbiol* 2016;1:1–2.
15 Wilkins LJ, Monga M, Miller AW. Defining dysbiosis for a cluster of chronic diseases. *Sci Rep* 2019;9.
16 Huseyin CE, O'Toole PW, Cotter PD, *et al*. Forgotten fungi—the gut mycobiome in human health and disease. *FEMS Microbiol Rev* 2017;41:479–511.
17 Reyes A, Haynes M, Hanson N, *et al*. Viruses in the faecal microbiota of monozygotic twins and their mothers. *Nature* 2010;466:334–8.
18 Khoruts A, Dicksved J, Jansson JK, *et al*. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent Clostridium difficile-associated diarrhea. *J Clin Gastroenterol* 2010;44:354–60.
19 Frank DN, St. Amand AL, Feldman RA, *et al*. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci U S A* 2007;104:13780–5.
20 Morgan XC, Tickle TL, Sokol H, *et al*. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol* 2012;13:R79.
21 Gophna U, Sommerfeld K, Gophna S, *et al*. Differences between tissue-associated intestinal microfloras of patients with Crohn's disease and ulcerative colitis. *J Clin Microbiol* 2006;44:4136–41.
22 Sokol H, Seksik P, Furet JP, *et al*. Low counts of Faecalibacterium prausnitzii in colitis microbiota. *Inflamm Bowel Dis* 2009;15:1183–9.
23 Machiels K, Joossens M, Sabino J, *et al*. A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut* 2014;63:1275–83.
24 Varela E, Manichanh C, Gallart M, *et al*. Colonisation by *Faecalibacterium prausnitzii* and maintenance of clinical remission in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2013;38:151–61.
25 Willing B, Halfvarson J, Dicksved J, *et al*. Twin studies reveal specific imbalances in the mucosa-associated microbiota of patients with ileal Crohn's disease. *Inflamm Bowel Dis* 2009;15:653–60.
26 Ohkusa T, Sato N, Ogihara T, *et al*. Fusobacterium varium localized in the colonic mucosa of patients with ulcerative colitis stimulates species-specific antibody. *J Gastroenterol Hepatol* 2002;17:849–53.
27 Gevers D, Kugathasan S, Denson LA, *et al*. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014;15:382–92.
28 Britton GJ, Contijoch EJ, Mogno I, *et al*. Microbiotas from humans with inflammatory bowel disease alter the balance of gut Th17 and RORγt+ regulatory T cells and exacerbate colitis in mice. *Immunity* 2019;50:212–24.
29 Segal JP, Ding NS, Worley G, *et al*. Systematic review with meta-analysis: the management of chronic refractory pouchitis with an evidence-based treatment algorithm. *Aliment Pharmacol Ther* 2017;45:581–92.
30 Pardi DS, D'Haens G, Shen B, *et al*. Clinical guidelines for the management of pouchitis. *Inflamm Bowel Dis* 2009;15:1424–31.
31 Kohyama A, Ogawa H, Funayama Y, *et al*. Bacterial population moves toward a colon-like community in the pouch after total proctocolectomy. *Surgery* 2009;145:435–47.
32 Reshef L, Kovacs A, Ofer A, *et al*. Pouch inflammation is associated with a decrease in specific bacterial taxa. *Gastroenterology* 2015;149:718–27.
33 Tyler AD, Knox N, Kabakchiev B, *et al*. Characterization of the gut-associated microbiome in inflammatory pouch complications following ileal pouch-anal anastomosis. *PLoS One* 2013;8:e66934.
34 Machiels K, Sabino J, Vandermosten L, *et al*. Specific members of the predominant gut microbiota predict pouchitis following colectomy and IpaA in UC. *Gut* 2017;66:79–88.
35 Segal JP, Oke S, Hold GL, *et al*. Systematic review: ileoanal pouch microbiota in health and disease. *Aliment Pharmacol Ther* 2018;47:466–77.
36 Betrapally NS, Gillevet PM, Bajaj JS. Gut microbiome and liver disease. *Translational Research* 2017;179:49–59.
37 Bajaj JS, Kassam Z, Fagan A, *et al*. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. *Hepatology* 2017;66:1727–38.
38 Duan Y, Llorente C, Lang S, *et al*. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. *Nature* 2019;575:505–11.
39 Bhattarai Y, Muniz Pedrogo DA, Kashyap PC. Irritable bowel syndrome: a gut microbiota-related disorder? *Am J Physiol Gastrointest Liver Physiol* 2017;312:G52–62.
40 Hugerth LW, Andreasson A, Talley NJ, *et al*. No distinct microbiome signature of irritable bowel syndrome found in a Swedish random population. *Gut* 2019. doi:10.1136/gutjnl-2019-318717. [Epub ahead of print: 10 Oct 2019].
41 Kosumi K, Mima K, Baba H, *et al*. Dysbiosis of the gut microbiota and colorectal cancer: the key target of molecular pathological epidemiology. *J Lab Precis Med* 2018;3:76.
42 Brennan CA, Garrett WS, Microbiota G. Inflammation, and colorectal cancer. *Annu Rev Microbiol* 2016;70:395–411.
43 Mima K, Sukawa Y, Nishihara R, *et al*. *Fusobacterium nucleatum* and T Cells in Colorectal Carcinoma. *JAMA Oncol* 2015;1:653–61.
44 Mima K, Nishihara R, Qian ZR, *et al*. *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. *Gut* 2016;65:1973–80.
45 Ferreira-Halder CV, Faria AVdeS, Andrade SS. Action and function of Faecalibacterium prausnitzii in health and disease. *Best Pract Res Clin Gastroenterol* 2017;31:643–8.
46 Guo S, Li L, Xu B, *et al*. A simple and novel fecal biomarker for colorectal cancer: ratio of Fusobacterium nucleatum to probiotics populations, based on their antagonistic effect. *Clin Chem* 2018;64:1327–37.
47 Sivan A, Corrales L, Hubert N, *et al*. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015;350:1084–9.
48 Alexander JL, Wilson ID, Teare J, *et al*. Gut microbiota modulation of chemotherapy efficacy and toxicity. *Nat Rev Gastroenterol Hepatol* 2017;14:356–65.
49 Fessas P, Possamai LA, Clark J, *et al*. Immunotoxicity from checkpoint inhibitor therapy: clinical features and underlying mechanisms. *Immunology* 2019;13141.

50 Routy B, Le Chatelier E, Derosa L, *et al*. Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. *Science* 2018;359:91–7.
51 Matson V, Fessler J, Bao R, *et al*. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018;359:104–8.
52 Gopalakrishnan V, Spencer CN, Nezi L, *et al*. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 2018;359:97–103.
53 Wang Y, Wiesnoski DH, Helmink BA, *et al*. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. *Nat Med* 2018;24:1804–8.
54 Staudacher HM, Whelan K. The low FODMAP diet: recent advances in understanding its mechanisms and efficacy in IBS. *Gut* 2017;66:1517–27.10.1136/gutjnl-2017-313750
55 Svolos V, Hansen R, Nichols B, *et al*. Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition. *Gastroenterology* 2019;156:1354–67.
56 Roberfroid M. Prebiotics: the concept revisited. *J Nutr* 2007;137:830S–7.
57 Gibson GR, Hutkins R, Sanders ME, *et al*. Expert consensus document: the International scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol* 2017;14:491–502.
58 Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr* 1995;125:1401–12.
59 Hoentjen F, Welling GW, Harmsen HJM, *et al*. Reduction of colitis by prebiotics in HLA-B27 transgenic rats is associated with microflora changes and immunomodulation. *Inflamm Bowel Dis* 2005;11:977–85.
60 Swennen K, Courtin CM, Delcour JA. Non-Digestible oligosaccharides with prebiotic properties. *Crit Rev Food Sci Nutr* 2006;46:459–71.
61 Zhuang X, Li T, Li M, *et al*. Systematic review and meta-analysis: short-chain fatty acid characterization in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2019;25:1751–63.
62 Gareau MG, Sherman PM, Walker WA. Probiotics and the gut microbiota in intestinal health and disease. *Nat Rev Gastroenterol Hepatol* 2010;7:503–14.
63 Yoshimatsu Y, Yamada A, Furukawa R, *et al*. Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. *WJG* 2015;21:5985–94.
64 Lamb CA, Kennedy NA, Raine T, *et al*. British Society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;68:s1–106.
65 Mimura T*et al*. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004;53:108–14.
66 Ford AC, Harris LA, Lacy BE, *et al*. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther* 2018;48:1044–60.
67 Ford AC, Moayyedi P, Chey WD, *et al*. American College of gastroenterology monograph on management of irritable bowel syndrome. *Am J Gastroenterol* 2018;113:1–18.
68 Quraishi MN, Widlak M, Bhala N, *et al*. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2017;46:479–93.
69 Hvas CL, Dahl Jørgensen SM, Jørgensen SP, *et al*. Fecal microbiota transplantation is superior to Fidaxomicin for treatment of recurrent Clostridium difficile infection. *Gastroenterology* 2019;156:1324–32.
70 Hamilton MJ, Weingarden AR, Sadowsky MJ, *et al*. Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012;107:761–7.
71 Kao D, Roach B, Silva M, *et al*. Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection. *JAMA* 2017;318:1985–93.
72 Faecal microbiota TR faecal microbiota transplant for recurrent ansplant for recurrent Clostridium difficile infection Clostridium difficile infection interventional procedure guidance, 2014. Available: https://www.nice.org.uk/guidance/ipg485/resources/faecal-microbiota-transplant-for-recurrent-clostridium-difficile-infection-1899869993554885 [Accessed 20 Mar 2017].
73 Public Health England. Updated guidance on the management and treatment of Clostridium difficile infection. *Public Heal Engl* 2013:1–29 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/321891/Clostridium_difficile_management_and_treatment.pdf (accessed 20 Mar 2017).
74 Mullish BH, Quraishi MN, Segal JP, *et al*. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 2018;67:1920–41.
75 Debast SB, Bauer MP, Kuijper EJ, *et al*. European Society of clinical microbiology and infectious diseases: update of the treatment guidance document for Clostridium difficile infection. *Clinical Microbiology and Infection* 2014;20:1–26.
76 McDonald LC, Gerding DN, Johnson S, *et al*. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the infectious diseases Society of America (IDSA) and Society for healthcare epidemiology of America (SheA). *Clin Infect Dis* 2018;31:431–55.
77 DeFilipp Z, Bloom PP, Torres Soto M, *et al*. Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant. *N Engl J Med* 2019;381:2043–50.
78 Terveer EM, van Gool T, Ooijevaar RE, *et al*. Human transmission of Blastocystis by fecal microbiota transplantation without development of gastrointestinal symptoms in recipients. *Clin Infect Dis* 2019. doi:10.1093/cid/ciz1122. [Epub ahead of print: 15 Nov 2019].
79 Cammarota G, Ianiro G, Kelly CR, *et al*. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* 2019;68:2111–21.
80 Allegretti JR, Mullish BH, Kelly C, *et al*. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. *The Lancet* 2019;394:420–31.
81 Costello SP, Soo W, Bryant RV, *et al*. Systematic review with meta-analysis: faecal microbiota transplantation for the induction of remission for active ulcerative colitis. *Aliment Pharmacol Ther* 2017;46:213–24.
82 Paramsothy S, Paramsothy R, Rubin DT, *et al*. Faecal microbiota transplantation for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohn's Colitis* 2017;11:1180–99.10.1093/ecco-jcc/jjx063
83 Quraishi MNN, Yalchin M, Blackwell C, *et al*. STOP-Colitis pilot trial protocol: a prospective, open-label, randomised pilot study to assess two possible routes of faecal microbiota transplant delivery in patients with ulcerative colitis. *BMJ Open* 2019;9.
84 Ianiro G, Eusebi LH, Black CJ, *et al*. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2019;50:240–8.
85 El-Salhy M, Hatlebakk JG, Gilja OH, *et al*. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled

study. *Gut* 2019. doi:10.1136/gutjnl-2019-319630. [Epub ahead of print: 18 Dec 2019].
86 Woodhouse CA, Patel VC, Goldenberg S, *et al*. Profit, a prospective, randomised placebo controlled feasibility trial of faecal mIcrobiota transplantation in cirrhosis: study protocol for a single-blinded trial. *BMJ Open* 2019;9:e023518.
87 Allegretti JR, Kassam Z, Carrellas M, *et al*. Fecal microbiota transplantation in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2019;114:1071–9.
88 Allegretti JR, Kassam Z, Mullish BH, *et al*. Effects of fecal microbiota transplantation with oral capsules in obese patients. *Clinical Gastroenterology and Hepatology* 2019. doi:10.1016/j.cgh.2019.07.006. [Epub ahead of print: 10 Jul 2019].
89 Vrieze A, Van Nood E, Holleman F, *et al*. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012;143:913–6.
90 Reijnders D, Goossens GH, Hermes GDA, *et al*. Clinical and translational report effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: a randomized double-blind placebo-controlled trial cell metabolism clinical and translational report effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: a randomized double-blind placebo-controlled trial. *Cell Metab* 2016;24:63–74.
91 de Groot P, Scheithauer T, Bakker GJ, *et al*. Donor metabolic characteristics drive effects of faecal microbiota transplantation on recipient insulin sensitivity, energy expenditure and intestinal transit time. *Gut* 2019. doi:10.1136/gutjnl-2019-318320. [Epub ahead of print: 30 May 2019].
92 Kang D-W, Adams JB, Gregory AC, *et al*. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome* 2017;5:10.
93 Huttner BD, de Lastours V, Wassenberg M, *et al*. A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant Enterobacteriaceae: a randomized clinical trial. *Clin Microbiol Infect* 2019;25:830–8.